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**SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF  
COPPER(II), NICKEL(II), COBALT(III) AND IRON(III) COORDINATION  
COMPOUNDS WITH 1-(2-HYDROXYPHENYL)ETHANONE  
N(4)-ALLYL-S-METHYLISOTHIOSEMICARBAZONE**

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The paper presents the synthesis of the 1-(2-hydroxyphenyl)ethanone N(4)-allyl-S-methylisothiosemicarbazone (HL) and seven coordination compounds of copper, nickel, cobalt and iron with this pro-ligand. The newly obtained compounds were investigated by IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy, elemental analysis, molar electric conductivity and magnetic susceptibility. For the synthesized compounds the antibacterial and antifungal activities *in vitro* were studied on a series of standard strains, such as *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae* and *Candida albicans*. The *in vitro* antiproliferative activity of the pro-ligand and complexes was screened on Hep-2, BxPC-3, RD cancer cells and normal MDCK cells. It was established that coordination compounds manifest better antiproliferative activity than the pro-ligand.

**Keywords:** coordination compounds, 1-(2-hydroxyphenyl)ethanone, isothiosemicarbazone, biological activity.

**SINTEZA, CARACTERIZAREA ȘI ACTIVITATEA BIOLOGICĂ A COMPUȘILOR  
COORDINATIVI AI CUPRULUI(II), NICHELULUI(II), COBALTULUI(III) ȘI AI FIERULUI(III)  
CU N(4)-ALIL-S-METILIZOTIOSEMICARBAZONA 1-(2-HIDROXIFENIL)ETANONEI**

În lucrare este descrisă sinteza N(4)-alil-S-metilizotiosemicarbazonei 1-(2-hidroxifenil)etanonei (HL) și a șapte compuși coordinațivi ai cuprului, nichelului, cobaltului și ai fierului cu acest ligand. Compușii noi obținuți au fost studiați cu ajutorul spectroscopiilor IR și RMN ( $^1\text{H}$  și  $^{13}\text{C}$ ), analizei elementale, conductivității molare și susceptibilității magnetice. Pentru compușii sintetizați a fost studiată *in vitro* activitatea antibacteriană și antifungică selectivă față de spectrul larg de tulpini standard de *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae* și *Candida albicans*. Cercetarea proprietăților antiproliferative *in vitro* ale ligandului și ale complexelor a fost testată pe celule canceroase Hep-2, BxPC-3, RD și celule normale MDCK. S-a stabilit că compușii coordinațivi manifestă o activitate mai bună decât ligandul.

**Cuvinte-cheie:** compuși coordinațivi, 1-(2-hidroxifenil)etanonă, izotiosemicarbazonă, activitate biologică.

## Introduction

Isothiosemicarbazones and their metal complexes manifest a wide range of biological properties such as antimicrobial, antifungal, antituberculous, cytotoxic activities [1-3]. However, there is a limited number of studies on S-alkylisothiosemicarbazones, in spite of their importance in selective biological activity. Most of the medicaments existing today have high toxicity, so the search for new substances with lower toxicity and more effective anticancer drugs are of great interest. Some 1-(2-hydroxyphenyl)ethanone 3-thiosemicarbazones are already described in scientific literature [4,5].

The aim of this work is finding the conditions of synthesis, determination of the composition and physico-chemical properties of the copper, nickel, cobalt and iron coordination compounds with 1-(2-hydroxyphenyl)ethanone N(4)-allyl-S-methylisothiosemicarbazone.

## Experiment

### Materials and methods

N(4)-allyl-3-thiosemicarbazide was synthesized by the reaction between allyl isothiocyanate and hydrazine hydrate [6]. 1-(2-hydroxyphenyl)ethanone (Sigma-Aldrich), metal salts were used as received.

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker DRX-400, using  $\text{CDCl}_3$  as a solvent. The chemical shifts ( $\delta$ ) in ppm were measured relative to tetramethylsilane (TMS). Infrared spectra of the compounds were recorded on a Bruker ALPHA FTIR spectrophotometer at room temperature in the range of 4000-400  $\text{cm}^{-1}$ .

Magnetochemical research was made at room temperature using Gouy method [7].

The determination of metal content in the synthesized coordination compounds, using titration methods, was performed similarly to the literature procedures [8-11].

Melting point of the pro-ligand was measured using capillary method [12].

Molar conductivity values were determined in  $10^{-3}$  mol/L methanol solutions using slidewire bridge R-38.

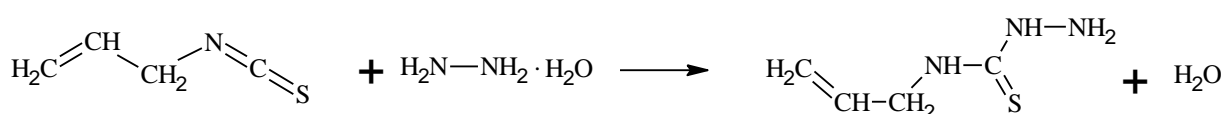
### Synthesis of the 4-allyl-3-thiosemicarbazide

4-Allyl-3-thiosemicarbazide (**Scheme 1**) was prepared similarly to the literature procedure [13].

White solid. Yield: 84%; m.p.: 91-93 °C; FW: 131.1994 g/mol;

Main IR peaks ( $\text{cm}^{-1}$ ):  $\nu(\text{N}^1\text{H}_2)$  3339, 3270;  $\nu(\text{N}^2\text{-H})$ ,  $\nu(\text{N}^4\text{-H})$  3189, 3162;  $\nu(\text{C}=\text{C}$  allyl) 1641;  $\nu(\text{C}=\text{S})$  1226.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ;  $\delta$ , ppm): 8.71 (br, 1H, NH); 7.54 (br, 1H, NH); 5.73 (m, 1H, CH from allyl moiety); 5.25 (m, 2H,  $\text{CH}_2=\text{C}$ ); 4.28 (m, 2H,  $\text{CH}_2\text{-N}$ ); 3.78 (br, 2H,  $\text{NH}_2$ ).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ;  $\delta$ , ppm): 177.51 (C=S); 132.43 (CH from allyl moiety); 116.15 ( $\text{CH}_2=$ ); 46.77 ( $\text{CH}_2\text{-N}$ ).

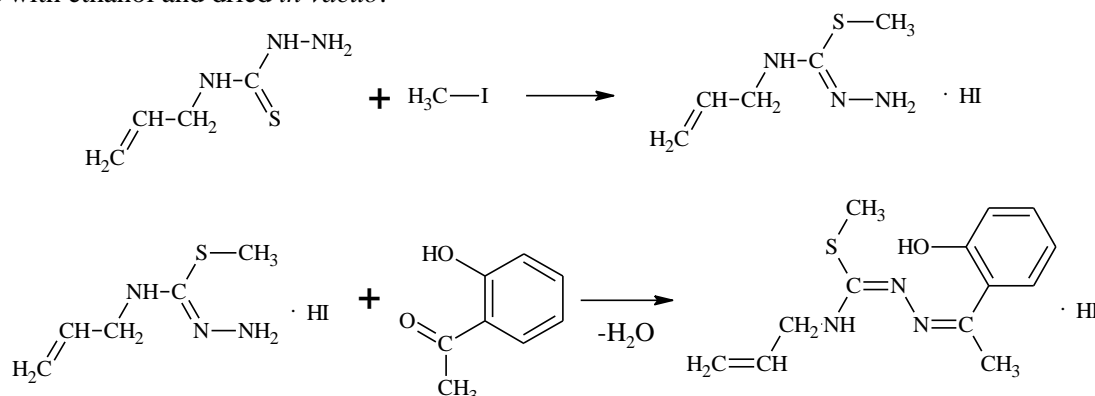


**Scheme 1.** Synthesis of the 4-allyl-3-thiosemicarbazide.

### Synthesis of the 1-(2-hydroxyphenyl)ethanone N(4)-allyl-S-methylisothiosemicarbazone (HL)

1-(2-Hydroxyphenyl)ethanone N(4)-allyl-S-methylisothiosemicarbazone (HL) (**Scheme 2**) was prepared according to a modification of the procedure described in the literature [14].

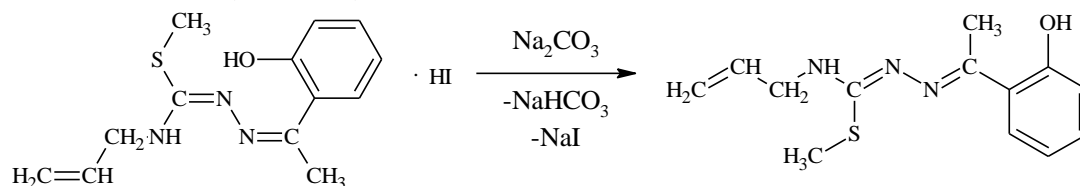
4-Allyl-3-thiosemicarbazide (1.31 g, 10 mmol) was dissolved in 20 mL of ethanol with constant stirring. After that iodomethane (1.56 g, 11 mmol) was added. The mixture was stirred at room temperature for 2 hours and 1-(2-hydroxyphenyl)ethanone (1.36 g, 10 mmol) was added. The solution was stirred at 80 °C for 30 min. After the reaction mixture was cooled to room temperature, the yellow solid was isolated by filtration, washed with ethanol and dried *in vacuo*.



**Scheme 2.** Synthesis of 1-(2-hydroxyphenyl)ethanone 4-allyl-S-methylisothiosemicarbazone hydroiodide.

Sodium carbonate (1.06 g, 10 mmol) was added to the solution of 1-(2-hydroxyphenyl)ethanone 4-allyl-S-methylisothiosemicarbazone hydroiodide (3.91 g, 10 mmol).

After the reaction mixture was cooled to room temperature, the 1-(2-hydroxyphenyl)ethanone 4-allyl-S-methylisothiosemicarbazone was extracted with chloroform from the reaction mixture. After evaporation yellow solid was obtained (**Scheme 3**).



**Scheme 3.** Neutralization of 1-(2-hydroxyphenyl)ethanone 4-allyl-S-methylisothiosemicarbazone hydroiodide.

Yellow solid. Yield: 80%; m.p.: 50-52 °C; FW: 263.36 g/mol;

Main IR peaks (cm<sup>-1</sup>): ν(OH) 3387, ν(C=C allyl) 1644, ν(C=N<sup>1</sup>) 1595, ν(C-O) 1245, ν(CH<sub>3</sub>-S) 1067, ν(C-S) 622.

1<sup>st</sup> tautomeric form (**HL(A)** on **Scheme 4**): <sup>1</sup>H NMR (CDCl<sub>3</sub>; δ, ppm): 13.51 (br, 1H, OH); 7.50 (d, 1H, CH aromatic); 7.26 (t, 1H, CH aromatic); 6.96 (d, 1H, CH aromatic); 6.86(t, 1H, CH aromatic); 5.87 (m, 1H, CH from allyl moiety); 5.52 (br, 1H, NH); 5.19 (m, 2H, CH<sub>2</sub>=C); 3.9 (m, 2H, CH<sub>2</sub>-N); 2.49 (s, 3H, CH<sub>3</sub>-S); 2.41 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>; δ, ppm): 159.71 (C-S); 163.77, 134.06, 128.25, 120.43, 118.74, 117.11 (C aromatic); 159.40 (CH<sub>3</sub>-C<sup>\*</sup>=N); 130.83 (CH from allyl moiety); 116.80 (CH<sub>2</sub>=); 45.80 (CH<sub>2</sub>-N); 13.77 (CH<sub>3</sub>); 13.19 (CH<sub>3</sub>-S).

2<sup>nd</sup> tautomeric form (**HL(B)** on **Scheme 4**): <sup>1</sup>H NMR (CDCl<sub>3</sub>; δ, ppm): 13.51 (br, 1H, OH); 7.51 (d, 1H, CH aromatic); 7.23 (t, 1H, CH aromatic); 6.98 (d, 1H, CH aromatic); 6.86 (t, 1H, CH aromatic); 5.98 (m, 1H, CH from allyl moiety); 5.22 (m, 2H, CH<sub>2</sub>=C); 4.60 (br, 1H, NH); 4.08 (m, 2H, CH<sub>2</sub>-N); 2.50 (s, 3H, CH<sub>3</sub>-S); 2.40 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>; δ, ppm): 159.54 (C-S); 161.77, 134.14, 127.97, 120.27, 118.40, 117.28 (C aromatic); 159.31 (CH<sub>3</sub>-C<sup>\*</sup>=N); 130.46 (CH from allyl moiety); 117.05 (CH<sub>2</sub>=); 46.20 (CH<sub>2</sub>-N); 13.56 (CH<sub>3</sub>); 13.23 (CH<sub>3</sub>-S).

### Synthesis of coordination compounds

The complexes (I-IV) were obtained by stirring a hot solution of **HL** in ethanol with the corresponding copper and nickel salts in 1:1 molar ratio: CuCl<sub>2</sub>·2H<sub>2</sub>O (**I**), Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O (**II**), Cu(CH<sub>3</sub>COO)<sub>2</sub>·H<sub>2</sub>O (**III**), Ni(CH<sub>3</sub>COO)<sub>2</sub>·4H<sub>2</sub>O (**IV**). Cobalt and iron coordination compounds (**V-VII**) were synthesized similarly, but in 1:2 molar ratio: Co(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O (**V**), CoBr<sub>2</sub>·6H<sub>2</sub>O (**VI**), Fe(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O (**VII**). After cooling green (in case of complexes **I-III**) or brown (in case of complexes **IV-VII**) precipitates of corresponding coordination compounds were filtered, washed with small amounts of cold ethanol and dried.

### Biological studies

#### Antibacterial bioassay

The antibacterial activity of complexes was determined under liquid nutritive environment [2% of peptone bullion (pH 7.0)] using successive dilutions method. *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae* standard stems were used as reference culture for in vitro experiment. The dissolution of studied substances in dimethyl sulfoxide, microorganisms' cultivation, suspension obtaining, determination of minimal inhibition concentration (MIC) and minimal bactericide concentration (MBC) were carried out according to the previously reported method.

#### Antifungal bioassay

Antimycotic properties of the synthesized substances were investigated *in vitro* on laboratory stems of *Candida albicans*. The activity was determined in liquid Sabouroud nutritive environment (pH 6.8). The inoculates were prepared from fungi stems which were harvested during 3-7 days. Their concentration in suspension is (2-4) or 10<sup>6</sup> colonies forming units/mh. Sowings for levures and micelles were incubated at 37 °C during 7 and 14 days, respectively.

#### Cell proliferation assay of Hep-2, BxPC-3, RD cells

Cells were trypsinized Trypsin-ethylenediaminetetraacetic acid (trypsin-EDTA) 0.05% (Invitrogen) and counted under an inverted microscope (OLYMPUS). The cell proliferation assay was performed using resazurin (7-hydroxy-3H-phenoxazin-3-one-10-oxide sodium salt) (SIGMA), which allowed us to measure the number of viable cells.

In brief, plate out, in triplicate of 1·10<sup>4</sup> cells in a total of 100 μl medium in 96-well microtiter plates (Becton Dickinson and Company, Lincoln Park, NJ, USA) were incubated at 37°C, 2% CO<sub>2</sub>. Compounds were dissolved in dimethyl sulfoxide to prepare the stock solution of 10mM. These compounds and doxorubicin was diluted at multiple concentrations with culture media, added to each well and incubated for 24 hours. Following each treatment, 20 μL resazurin indicator solution was added to each well and incubated for 4 hours. Subsequently, the absorbance was read with 570 nm and 600 nm filters. The measurement was made by imaging hybrid reader (Synergy H1, Biotek).

The percentage inhibition was calculated according to the formula:

$$100 - ((\text{Abs}_{570\text{nm}}^{\text{sample}} - \text{Abs}_{600\text{nm}}^{\text{sample}}) / (\text{Abs}_{570\text{nm}}^{\text{control}} - \text{Abs}_{600\text{nm}}^{\text{control}})) \times 100$$

The IC<sub>50</sub> values were evaluated by statistical software.

### MDCK cell culture

Madin-Darby canine kidney cells of line MDCK (ATCC) p.3-4 and epitheloid cervix carcinoma cells of line HeLa p.4-6 (SIGMA) were used. They were cultured as monolayers in Dulbecco's Modified Eagle Medium (D-MEM) high glucose (Invitrogen) containing L-glutamine, bovine albumin fraction (V7.5%) 0,2% v/v (Invitrogen), HEPES buffer (N-2 hydroxyethylpiperazine-N'-2-ethane sulfonic acid) 20mM (Invitrogen), antibiotics penicillin-streptomycin (final concentration 100 U/mL penicillin and 100 μg/mL streptomycin sulfate) (Invitrogen) and supplemented with fetal bovine serum (FBS-irradiated) 10% v/v (Cambrex) in culture conditions (2% CO<sub>2</sub>, 78% air in humidified chamber at 37°C).

### Results and discussion

The pro-ligand **HL** and seven new metal complexes were synthesized in ethanol in good yield. The structure and purity of **HL** were determined by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. All complexes were prepared by the direct reaction between the pro-ligand **HL** and the corresponding metal salts. The obtained coordination compounds are microcrystalline solids and are stable in air. The elemental analyses on copper, nickel, cobalt and iron suggest the general formulae M(L)X (M=Cu<sup>2+</sup>, Ni<sup>2+</sup>; X=Cl, Br, NO<sub>3</sub>, CH<sub>3</sub>COO<sup>-</sup>) and M(L)<sub>2</sub>X (M=Co<sup>3+</sup>, Fe<sup>3+</sup>; X=Br, NO<sub>3</sub><sup>-</sup>).

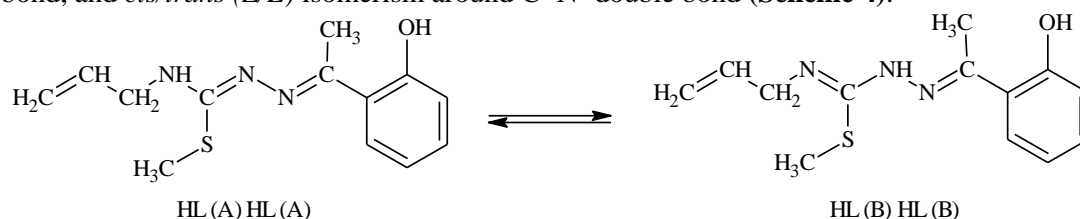
Table 1

Physical and analytical data of the metal complexes (I-VII)

No.	Compound	Formula	η <sup>a</sup> , %	Found /calculated, metal %	μ <sub>eff</sub> <sup>b</sup> , MB	λ <sup>c</sup>
I	Cu(L)Cl	C <sub>13</sub> H <sub>16</sub> ClCuN <sub>3</sub> OS	75	17.23/17.59	1.96	88
II	Cu(L)NO <sub>3</sub>	C <sub>13</sub> H <sub>16</sub> CuN <sub>4</sub> O <sub>4</sub> S	89	16.72/16.38	1.78	101
III	Cu(L)OAc	C <sub>15</sub> H <sub>19</sub> CuN <sub>3</sub> O <sub>3</sub> S	71	16.88/17.04	1.83	102
IV	Ni(L)OAc	C <sub>15</sub> H <sub>19</sub> N <sub>3</sub> NiO <sub>3</sub> S	74	15.20/15.44	dia <sup>d</sup>	85
V	Co(L) <sub>2</sub> NO <sub>3</sub>	C <sub>26</sub> H <sub>32</sub> CoN <sub>7</sub> O <sub>5</sub> S <sub>2</sub>	80	8.92/9.13	dia <sup>d</sup>	98
VI	Co(L) <sub>2</sub> Br	C <sub>26</sub> H <sub>32</sub> BrCoN <sub>6</sub> O <sub>2</sub> S <sub>2</sub>	83	8.59/8.88	dia <sup>d</sup>	109
VII	Fe(L) <sub>2</sub> NO <sub>3</sub>	C <sub>26</sub> H <sub>32</sub> FeN <sub>7</sub> O <sub>5</sub> S <sub>2</sub>	88	8.15/8.69	5.75	75

a – yield; b – effective magnetic moments at room temperature (293K); c – molar conductivity in methanol at room temperature, Ω<sup>-1</sup>·cm<sup>2</sup>·mol<sup>-1</sup>; d – diamagnetic.

In the NMR spectra all peaks of isothiosemicarbazone **HL** are double [15]. It indicates the presence of tautomeric forms of isothiosemicarbazone in solution. The integral ratio between two tautomeric forms is 1:3.3 (**HL(A)**:**HL(B)**). The presence of tautomeric forms can be caused by *syn/anti* isomerism around C=N<sup>1</sup> double bond, and *cis/trans* (*Z/E*) isomerism around C=N<sup>4</sup> double bond (**Scheme 4**).

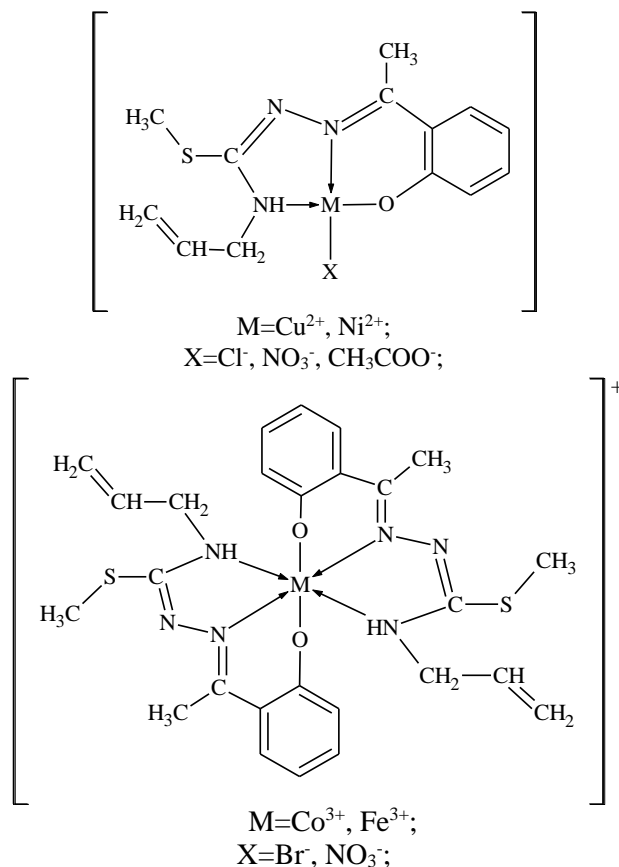


Scheme 4. The tautomeric forms of the pro-ligand **HL**.

The molar conductivity values of the synthesized complexes (**I-VII**) are in the range 75 - 109 Ω<sup>-1</sup>·cm<sup>2</sup>·mol<sup>-1</sup> that indicates that complexes (**I-VII**) represent 1:1 electrolytes [16, 17]. The corresponding anion (Cl<sup>-</sup>, Br<sup>-</sup>, NO<sub>3</sub><sup>-</sup>, CH<sub>3</sub>COO<sup>-</sup>) can be either in the outer sphere or in the inner sphere as it can be easily substituted by the solvent molecule during dissolution process.

The magnetochemical research showed that the synthesized copper coordination compounds (**I-III**) have monomeric structure because the effective magnetic moments for the synthesized complexes **I-III** vary in the range of 1.78-1.96 μ<sub>B</sub> which are close to the spin value for one unpaired electron. The nickel complex (**IV**) is diamagnetic that indicates that this coordination compound has square-planar coordination geometry. The cobalt and iron coordination compounds have octahedral structure. The cobalt complexes (**V-VI**) are diamagnetic that indicates that cobalt (**II**) is oxidized by oxygen from air to cobalt (**III**) during the synthesis.

The synthesis of the complexes is reproducible and the isothiosemicarbazone **HL** coordinates as a mono-negative tridentate ligand with ONN-set of donor atoms. Type of the ligand coordination with the central ions was elucidated from comparative analysis of IR spectra of complexes (**I-VII**) and the pro-ligand **HL**. It coordinates to the central ions by deprotonated phenolic oxygen atom, azomethinic and thiocarbamide nitrogen atoms forming five- and six-membered metallacycles. The proposed distribution of chemical bonds in the coordination compounds is shown in scheme 5.



**Scheme 5.** Proposed distribution of chemical bonds in the metal complexes.

For the synthesized compounds the antibacterial and antifungal activities *in vitro* were studied on a series of standard strains. The study of antibacterial and antifungal activities (**Table 2**) showed that **HL** and its coordination compounds possess bacteriostatic and bactericidal activities. The activity of the synthesized compounds towards gram-negative microorganisms is less pronounced than towards gram-positive bacteria and fungi.

**Table 2**

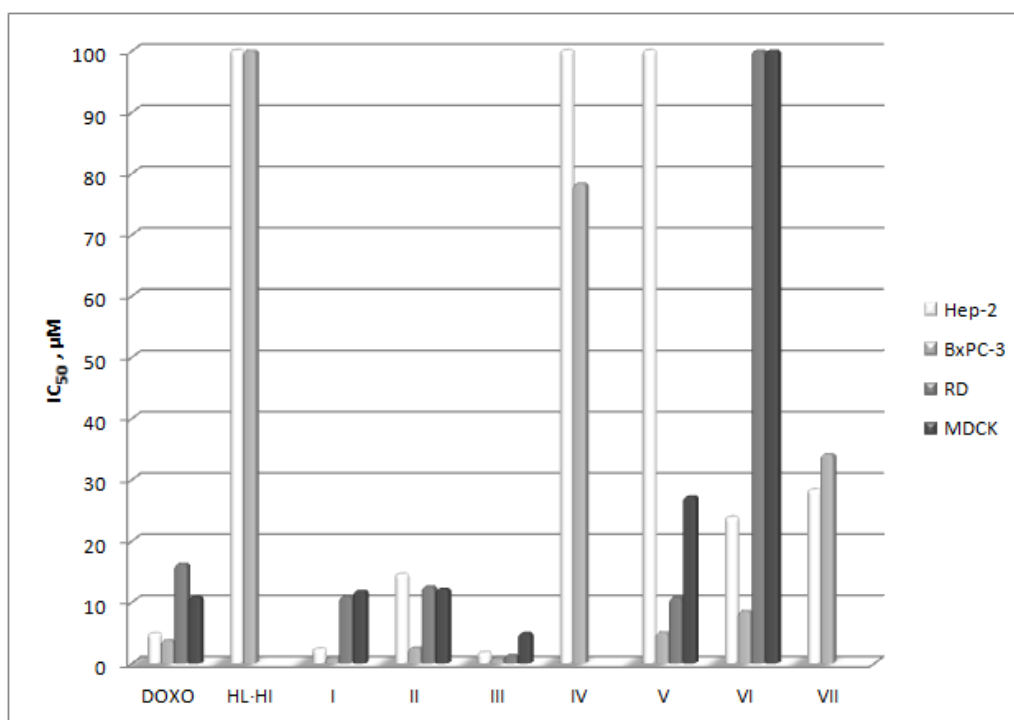
**The minimum inhibitory concentration (MIC) and minimum bactericide concentration (MBC) (mg/mL)**

Compound	<i>Escherichia coli</i> , ATCC 25922		<i>Staphylococcus aureus</i> , ATCC 25923		<i>Klebsiella pneumoniae</i>		<i>Candida albicans</i>	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
<b>HL</b> ·HI	0.5	0.5	0.03	0.06	0.5	0.5	0.06	0.06
<b>I</b>	0.12	0.12	0.03	0.06	0.12	0.12	0.03	0.03
<b>II</b>	0.03	0.06	0.03	0.06	0.25	0.5	0.03	0.03
<b>III</b>	0.12	0.12	0.03	0.06	0.12	0.12	0.03	0.03
<b>IV</b>	0.5	0.05	0.03	0.06	0.5	0.5	0.03	0.03
<b>V</b>	0.5	0.05	0.03	0.06	0.5	0.5	0.03	0.03
<b>VI</b>	0.5	0.05	0.03	0.06	0.5	0.5	0.03	0.03
<b>VII</b>	0.5	0.5	0.03	0.06	0.5	0.5	0.03	0.03

The **HL**·HI and coordination compounds show selective antimicrobial and antifungal activity towards a series of standard strains *Staphylococcus aureus* (ATCC 25923), *Escherihia coli* (ATCC 25922), *Klebsiella pneumoniae*, and *Candida albicans* in the range of concentration 0.03-0.5 mg/mL. It was found that the copper complexes are the most active ones. The comparison of antibacterial and antifungal activities of these compounds against the selected types of bacteria indicates that the activity of the coordination compounds decreases in the following way Cu(II) > Fe(III)  $\approx$  Co(III)  $\approx$  Ni(II).

It was also studied the antitumor activity of the pro-ligand and complexes on Hep-2, BxPC-3, RD cancer cells and normal MDCK cells.

In order to find out the biological properties it was studied the antitumor activity of the 1-(2-hydroxyphenyl)ethanone N(4)-allyl-S-methylisothiosemicarbazone (**HL**) and its coordination compounds. The  $IC_{50}$  values of these substances are shown in scheme 6.



Scheme 6.  $IC_{50}$  values of tested substances.

It was determined that the studied copper, cobalt and iron coordination compounds are more active than the pro-ligand and nickel complex. The complexes **I** and **III** manifest better activity than doxorubicine that is used in medical practice.

The study of the influence of synthesized compounds on healthy MDCK cells, showed that they have lower cytotoxic effect on healthy cells of human organism. The cobalt complexes (**V-VI**) showed promising antiproliferative activity and low toxicity.

### Conclusions

In this work 1-(2-hydroxyphenyl)ethanone N(4)-allyl-S-methylisothiosemicarbazone was synthesized and studied using NMR spectroscopy. This pro-ligand was used for synthesis of seven coordination compounds of copper, nickel, cobalt and iron. These compounds were studied using elemental analysis, molar conductivity, and magnetochemistry. The copper coordination compounds (**I-III**) have monomeric structure. The nickel (**IV**) complex is square-pyramidal, cobalt (**V-VI**) and iron (**VII**) complexes are octahedral. It was determined, that the coordination compounds show antibacterial and antifungal activities.

The synthesized compounds selectively inhibit the Hep-2, BxPC-3, RD cancer cells growth in the range of concentrations  $10^{-5}$ - $10^{-7}$  mol/L. The cobalt complexes (**V-VI**) inhibit proliferation of cancer cells and does not affect the growth of normal cells.

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